Claim 7 is amended herewith to conform the disorders listed therein to those of Claim 3 so Claim 7 should be allowable if Claim 3 is allowable.

Claim 8 is canceled herewith as being redundant in view of the amendments to Claim 7.

Claims 9 and 10 are canceled herewith to change the dependency from 8 to 7 in view of the cancellation of Claim 8.

Claim 11 has been amended to include limitations of Claim 17 and to correct an error.

Claim 17 has been amended to include the limitations of canceled Claim 6 and to change the dependency in view of cancellation of Claim 6.

A version with markings to show changes made is attached.

We turn now to the rejections.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph. Claim 6 is canceled herewith to reduce the issues. Reconsideration is requested.

Claims 1 and 2 are rejected under 35 U.S.C. 102(a) as being anticipated by Gregory, et al WO 07/297,776. Claims 1 and 2 are canceled herewith to reduce the issues. Reconsideration is required.

Claims 1-6 and 17 were rejected as being obvious over Gregory, et al. U.S. Patent No. 6,172,096 in view of Talley U.S. Patent No. 5,643,933. The office action takes the position that even though Gregory does not expressly teach the treatment of liver diseases listed in Claim 3, it would have been *prima facie* obvious to a person of ordinary skill in the art to employ the specified compounds for treating hepatitis disease because those compounds are known generally to be useful for treating inflammatory diseases and are know to be useful for treating liver related diseases. In response to applicant's position that use of selective inhibitors of COX-2 wold not be

-3-

obvious for treatment of the named liver disorders because the FDA concluded in 1982 that

hepatotoxicity is a class characteristic of NSAIDs, the office action cites Seibert, et al. CAPLUS

Abstract, AN 1998:369098, and based thereon takes the position that one skilled in the art would

reasonably have expected that selective COX-2 inhibitors would not be hepatotoxic like

conventional NSAIDs.

Reconsideration of the obviousness rejection is requested in view of the positions below.

It is submitted that the hypothesis that in view of Seibert, et al. "one of ordinary skill in the

art would have reasonably expected that selective COX-2 inhibitors would not be hepato[to]xic

like conventional NSAIDs" is not well founded. Enclosed is a copy of an article cited as Swan,

S.K., et al, Ann. Inter. Med. 2000; 133:1-9 which concludes "The effects of COX-2 inhibitor on

renal function are similar to those observed with nonselective NSAIDs." This illustrates that

although selective inhibitors of COX-2 appear to cause less gastrointestinal toxicity than NSAIDs

(dual inhibitors of COX-1/COX-2), one can't extrapolate to other organ systems. Morever,

consider that abnormal liver chemistries have been observed in patients taking selective inhibitors

of COX-2. Consider further, that the PDR (2001) at page 2051 states:

> Use of VIOXX is not recommended in patients with moderate or severe
> hepatic insufficiency.

> Consider that the PDR (2001) at page 2484, states:

> If clinical signs and symptoms consistent with liver disease develop...
> CELEBREX should be discontinued.

Thus, it is submitted that the PDR in 2001 teaches against administration of selective inhibitor of

cyclooxygenase-2 to those with liver disease.

What is submitted to be unobvious is the discovery herein that there is a net benefit to administering selective inhibitors of cyclooxygenase-2 to those with liver diseases as claimed.

Consider further that while the prior art may teach a net benefit for treatment in respect to transplant rejection and autoimmune diseases, even though liver related, there is no such teaching in the prior art in respect to the diseases treated in the claims and it is submitted that there would therefore be no reasonable expectation of success from the prior art in the case of the claimed methods.

It is submitted that in view of the above, Claims 3-5 and 17 are unobvious over the applied prior art and therefore patentable.

It is submitted that since Claim 7 is conformed to Claim 3 in respect to disorders treated, Claims 7 and 9-11 as amended should also be patentable.

Entry of the amendments made herein and allowance of remaining Claims 3-5, 7, 9-11 and 17, is requested.

Respectfully submitted,

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703-415-1500   Case CRF D-2165

April 16, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claims 1, 2, 6 and 8 are canceled.

Claim 7 is amended as follows:

7.   (Amended) A method of treating a patient with a virus-caused liver disease selected from the group consisting of chronic viral hepatitis B and chronic viral hepatitis C comprising administering to said patient a cyclooxygenase-2 inhibiting amount of selective inhibitor of cyclooxygenase-2 and therapeutic amount(s) of anti-viral drug(s).

Claim 9 is amended as follows:

9.   (Amended) The method of Claim 7[8], wherein the selective inhibitor of cyclooxygenase-2 is 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

Claim 10 is amended as follows:

10.   (Amended) The method of Claim 7[8] wherein the selective inhibitor of cyclooxygenase-2 is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

Claim 11 is amended as follows:

11.   (Amended) The method of Claim 7[8] wherein the selective inhibitor of cyclooxygenase-2 directly inhibits the enzyme cyclooxygenase-2 and also inhibits the synthesis of cyclooxygenase-2 protein and contains phenyl group with two or more substituents selected from the group consisting of hydroxy and C_{1-4}-alkoxy on the phenyl group.

-6-

Claim 17 is amended as follows:

17. (Amended) The method of Claim 3[6] wherein the selective inhibitor of

cyclooxygenase-2 directly inhibits the enzyme cyclooxygenase-2 and also inhibits the synthesis of

cyclooxygenase-2 protein and contains phenyl group with two or more substituents selected from

the group consisting of hydroxy and C_{1-4}-alkoxy on the phenyl group.

Effect of Cyclooxygenase-2 Inhibition on Renal Function in Elderly Persons Receiving a Low-Salt Diet

A Randomized, Controlled Trial

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Background: Most nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both cyclooxygenase-1 (COX-1), whose inhibition is associated with gastrointestinal ulceration, and COX-2, whose inhibition is associated with therapeutic benefits. Although agents that do not produce COX-1 activity may have fewer adverse effects, targeted disruption of the COX-2 allele in mice has resulted in severe renal problems, suggesting that COX-2 inhibition may also produce adverse effects.

Objective: To determine the effect of rofecoxib, a member of the coxib class of drugs and a specific inhibitor of the COX-2 enzyme, on renal function in elderly patients.

Design: A randomized, three-period, single-dose crossover study and a randomized, parallel-group, multiple-dose study.

Setting: Clinical research units.

Patients: 75 patients 60 to 80 years of age.

Intervention: In the first study, single doses of rofecoxib, 250 mg (about 5-fold to 20-fold the recommended dose); indomethacin, 75 mg; and placebo were administered to 15 patients. In the second study, multiple doses of rofecoxib, 12.5 or 25 mg/d; indomethacin, 50 mg three times daily; or placebo were administered to 60 patients. Patients in both studies received a low-sodium diet.

Measurements: Glomerular filtration rate, creatinine clearance, and urinary and serum sodium and potassium values.

Results: Compared with placebo, single doses of rofecoxib and indomethacin decreased the glomerular filtration rate by 0.23 mL/s ($P < 0.001$) and 0.18 mL/s ($P = 0.003$), respectively. In contrast, respective decreases of 0.14, 0.13, and 0.10 mL/s were observed after multiple doses of rofecoxib, 12.5 mg/d ($P = 0.019$); rofecoxib, 25 mg ($P = 0.029$); and indomethacin ($P = 0.086$) were administered. Changes in creatinine clearance and serum and urinary sodium and potassium were less pronounced.

Conclusions: The effects of COX-2 inhibition on renal function are similar to those observed with nonselective NSAIDs. Thus, COX-2 seems to play an important role in human renal function.

The effects of nonsteroidal anti-inflammatory drugs (NSAIDs) are mediated through their ability to inhibit cyclooxygenase (COX)-catalyzed prostaglandin production. Two isoforms of COX, COX-1 and COX-2, have been identified (1–4); traditional NSAIDs inhibit both isoforms (5). Cyclooxygenase-1 is constitutively expressed throughout the body and is thought to play an essential role in normal gastrointestinal and platelet function, whereas COX-2 is induced in the presence of inflammation. Inhibition of COX-1 is thought to cause the adverse gastrointestinal effects associated with NSAID therapy, whereas inhibition of COX-2 has been associated with the therapeutic effects of NSAIDs (6). When administered at therapeutic doses, rofecoxib inhibits only the COX-2 isoform (7).

Common renal adverse effects of traditional NSAIDs (which inhibit renal COX-1 and COX-2) are reductions in glomerular filtration rate, renal blood flow, and sodium and potassium excretion. These effects can lead to fluid retention, edema, hypertension, and hyperkalemia. The degree to which inhibition of COX-1 compared with inhibition of COX-2 may be responsible for different NSAID-associated nephrotoxicities has not been clearly delineated. Studies in animals and humans demonstrate the constitutive presence of COX-2 in the kidney, which suggests that COX-2 may play a substantial role in renal function (8, 9). A recent study in healthy volunteers indicated a renal effect of COX-2 inhibition with celecoxib, although it was unknown whether this was a drug-specific or class effect (10).

We studied a range of doses of rofecoxib, a drug that specifically inhibits COX-2, and examined clinical conditions that are known to be associated with susceptibility to adverse renal effects of NSAIDs. To determine the effects

of COX-2 inhibition on glomerular filtration rate and serum and urine electrolyte balance, we administered rofecoxib to elderly patients who were receiving a sodium-restricted diet, which enhanced renal dependence on prostaglandin production (11, 12). The non–isoform-specific COX-1/COX-2 inhibitor indomethacin was included as a comparator to determine the relative clinical importance of inhibiting both COX isoforms.

Methods

The protocols were approved by the institutional review board at each site, and each patient provided written informed consent. Patients were nonsmokers in good general health who had a body mass index of 34 kg/m^2 or less. Patients with thyroid disease; allergy to iodine; or a history of substantial cardiovascular disease, diabetes, hypertension requiring treatment, hepatic disease, sodium-losing nephropathy, NSAID-induced renal failure, or peptic ulcer disease were excluded. Patients who received immunosuppressant therapy (including steroids) within 3 months before entry or a history of bladder outlet obstruction or urinary retention (including benign prostatic hyperplasia) within 6 months of study entry were also excluded. Concomitant use of diuretics, misoprostol, or any drug known to affect renal function, as well as low-dose aspirin or any NSAIDs, was prohibited. Randomization was done by using a computer-generated allocation schedule. Placebo was identical in appearance to the active drug, and only the person who packaged the supplies at Merck Research Laboratories was unblinded.

Single-Dose Study

The single-dose study had a three-period balanced crossover design. Patients 60 to 80 years of age who had creatinine clearance of at least 40 mL/min were enrolled at a single center (Indiana University). Before each study period, patients received a diet that included 43 mEq of sodium per day for 3 days; they then received a diet consisting of 30 mEq of sodium, 60 to 80 mEq of potassium, and 80 g protein for 3 more days (study days −6 to −1). If patients had a stable body weight (change ≤ 0.5 kg) on days −2 and −1, they were randomly assigned to double-blind, double-dummy treatment with single doses of rofecoxib, 250 mg; indomethacin, 75 mg; or placebo. At the time that this study was performed, clinical data demonstrating the effectiveness of rofecoxib at doses as low as

12.5 mg were not yet available. The 250-mg dose was chosen to "load" patients in a manner similar to that achieved with the 75-mg dose of indomethacin while maintaining COX-2 selectivity (7). The glomerular filtration rate was calculated by measuring inulin clearance before and after each treatment.

Multiple-Dose Study

Patients 65 to 80 years of age with creatinine clearance of 30 to 80 mL/min were enrolled at four centers (Hennepin County Medical Center and Total Renal Research, Inc.; Clinical Pharmacology Associates; PPD; and Indiana University). For 8 days (study days −8 to −1), they received a diet consisting of 30 mEq of sodium, 60 to 80 mEq of potassium, and 80 g of protein. Patients with a stable body weight (change ≤ 0.5 kg) on days −2 and −1 received a single-blind dose of placebo and underwent baseline measurement of iothalamate clearance to calculate the glomerular filtration rate. After the glomerular filtration rate was obtained, patients were randomly assigned to receive rofecoxib, 12.5 mg/d; rofecoxib, 25 mg/d; indomethacin, 50 mg three times daily; or placebo for 5 days. Assignments were made in a double-blind, double-dummy manner using a parallel-group design. Patients continued to receive a low-sodium diet. On the sixth day of drug administration (day 6), the glomerular filtration rate was calculated again after the first dose of drug or placebo was given for that day.

Inulin, Iothalamate, and Creatinine Clearances

Inulin was prepared and analyzed according to standard methods (13). A loading dose of 10% inulin, 0.25 mL/kg, was administered, followed by a 6-hour sustaining continuous intravenous infusion of 0.45 mL per mL/min of creatinine clearance, as determined previously. ^{125}I-Iothalamate (4-mL vials, Cypros Pharmaceuticals, Carlsbad, California) was used in the multicenter study because of ease of handling. ^{125}I-Iothalamate has been shown to be an excellent determinant of glomerular filtration rate compared with inulin (14, 15). A 30-μCi priming dose of ^{125}I-iothalamate was administered, followed by a 6-hour sustaining continuous intravenous infusion of 120-μCi, for a total dose of 150 μCi.

In both studies, patients fasted from midnight the night before until lunchtime on the day of glomerular filtration rate determination. During measurement of the

glomerular filtration rate, patients remained semirecumbent except during scheduled spontaneous voids (no catheters were placed). After receiving a loading dose of inulin or iothalamate, patients drank water, 10 mL/kg, to stimulate urine flow; flow was subsequently maintained by continuous intravenous infusion of a 5% dextrose solution in a volume equal to urinary losses plus 15 mL every 30 minutes. Drug was administered after equilibration was complete (urine output of >75 mL during two consecutive 30-minute collection periods).

Blood and urine specimens for measurement of inulin or iothalamate, creatinine, sodium, and potassium were obtained every 30 minutes starting at least 2 hours before drug administration (equilibration period) and until 6 hours afterward. Thereafter, samples were obtained 8, 10, 12, 16, and 24 hours after drug administration. Body weight, urinary electrolyte balance, creatinine clearance, and vital signs (including orthostatic changes) were monitored daily.

Because the pharmacokinetics of rofecoxib and indomethacin differ and peak effects would be expected to occur at different times, inulin and iothalamate clearances were measured every 30 minutes for the 6 hours after drug administration. The following formula was used: $Cl = (U \times V)/S$, where Cl is clearance, U is the urinary concentration of inulin or creatinine (or iothalamate counts), V is the urine flow rate (measured as mL/s), and S is the serum concentration of inulin or creatinine (or iothalamate counts).

The minimum glomerular filtration rate was defined as the lowest mean value observed in the moving average values obtained at three consecutive 30-minute intervals after drug administration. In the single-dose study, peak reduction from baseline was defined as the maximal difference between the minimum glomerular filtration rate after drug administration and the mean glomerular filtration rate measured during urinary stabilization (baseline). For the multiple-dose study, peak reduction in glomerular filtration rate was defined as the difference between the minimum glomerular filtration rate obtained after placebo administration on day −1 and the minimum glomerular filtration rate obtained after drug administration on day 6.

Urinary and Serum Sodium and Potassium

Urinary sodium excretion was calculated as follows: [100 × urine volume (L) × urinary sodium (mmol/L)]/ [difference in collection time (seconds)]; thus, the final values are expressed as 100 × mmol Na/s. A similar equation was used to convert the urinary potassium volume to urinary potassium excretion values.

Statistical Analysis

Data were forwarded to the statistics department at Merck Research Laboratories, and analyses were based on the treatment received. In the single-dose study, an analysis of covariance model was used. Carryover effects were tested and found to be nonsignificant ($P > 0.2$). The final model included terms for patient, period, treatment, sequence, and predose value as covariates. The final analysis of covariance model for the multiple-dose parallel-group study included factors for treatment, site, and the minimum glomerular filtration rate on day −1 (baseline). Similar analyses were used for absolute and average changes in inulin or iothalamate clearance, creatinine clearance, urinary sodium excretion, urinary potassium excretion, and serum levels of sodium and potassium.

The normality and homogeneity of variance assumptions of the analysis of covariance models were tested by using the Shapiro–Wilk statistic and the Levene test, respectively. Unless otherwise stated, all tests were two-sided at an α level of 0.05.

The primary hypothesis of the single-dose study was that rofecoxib, 250 mg, and indomethacin, 75 mg, would have similar effects in terms of peak reduction in inulin clearance. The study had 80% power to demonstrate that the 90% CI for the mean difference between rofecoxib and indomethacin in peak reduction in inulin clearance would fall between −17.1 and 17.1 mL/min, assuming that the true mean difference was zero. The primary hypothesis of the multiple-dose study was that rofecoxib, 25 mg, would reduce the glomerular filtration rate by 25% or more compared with placebo. For this study, we had 80% power to detect a between-treatment difference of at least 25% in mean peak reduction in iothalamate clearance.

Role of the Funding Source

The studies were funded and coordinated by Merck Research Laboratories, which reviewed this manuscript and was given the opportunity to delete any information deemed confidential. No data were deleted. The material was also reviewed by the U.S. Food and Drug Administration during marketing approval for rofecoxib.

Table 1. **Baseline Characteristics**

Characteristic	Single-Dose Study (n = 15)	Multiple-Dose Study			
		Placebo (n = 15)	Rofecoxib, 12.5 mg/d (n = 15)	Rofecoxib, 25 mg/d (n = 15)	Indomethacin, 50 mg Three Times Daily (n = 15)
Sex, n (%)					
Female	8 (46.7)	6 (40.0)	6 (40.0)	8 (53.3)	11 (73.3)
Male	7 (53.3)	9 (60.0)	9 (60.0)	7 (46.7)	4 (26.7)
Ethnicity, n (%)					
White	15 (100)	9 (60.0)	7 (46.7)	10 (66.7)	12 (80.0)
Black	0 (0)	0 (0)	0 (0)	0 (0)	2 (13.3)
Hispanic American	0 (0)	6 (40.0)	8 (53.3)	5 (33.3)	1 (6.7)
Mean screening creatinine clearance (range), mL/s	1.77 (1.17–2.57)	1.05 (0.55–1.25)	1.15 (0.77–1.32)	1.08 (0.73–1.32)	1.09 (0.84–1.34)
Mean body mass index (range), kg/m²	26.61 (22.26–32.76)	26.32 (20.72–32.15)	29.45 (24.62–34.01)	28.21 (23.41–33.82)	27.29 (20.52–33.82)
Mean age (range), y	68.3 (62–79)	72.5 (65–80)	70.6 (65–78)	72.1 (66–80)	72.2 (65–78)

Results

Single-Dose Study

Sixteen patients were enrolled, of whom 15 (7 men and 8 women) completed the study (Table 1). One patient was excluded before receiving the study drug because of abnormal laboratory values.

The mean predose and postdose inulin clearance values in the single-dose studies are shown in Table 2. Compared with placebo, rofecoxib and indomethacin produced significantly greater reductions in the peak glomerular filtration rate (0.23 and 0.18 mL/s, respectively; $P < 0.001$ and $P = 0.003$). The differences between peak glomerular filtration rate with rofecoxib and that with indomethacin were not significant ($P > 0.2$).

Serum and urine creatinine were also assayed to determine the effect of rofecoxib, indomethacin, and placebo on creatinine clearance. Consistent with the effects observed on inulin clearance, both rofecoxib and indomethacin caused significant peak reductions in creatinine clearance compared with placebo (0.32 and 0.19 mL/s, respectively; $P = 0.002$ and 0.051). Rofecoxib did not significantly differ from indomethacin in this regard ($P = 0.16$).

Table 3 shows the results of the various treatments on urinary and serum values for sodium and potassium. The reductions in urinary sodium excretion produced by rofecoxib and indomethacin differed significantly from those seen with placebo (68.35% and 48.95%, respectively; $P < 0.001$ and $P = 0.005$). The peak reduction in urinary potassium excretion after drug administration was significant only for rofecoxib compared with placebo (11.28%; $P = 0.012$).

At its peak effect, indomethacin significantly reduced serum sodium concentrations by 1.17% compared with placebo ($P = 0.005$). The reduction in serum sodium concentrations produced by rofecoxib compared with placebo was similar but not statistically significant (0.75%; $P = 0.059$). At peak effect, both rofecoxib and indomethacin increased serum potassium concentrations (by 2.30% and 4.19%, respectively; $P = 0.04$ and 0.001). The mean difference between rofecoxib and indomethacin in peak increase in serum potassium concentration was 1.89 percentage points ($P = 0.098$).

Multiple-Dose Study

A total of 71 patients were enrolled, of whom 60 (30 men and 30 women) completed the multiple-dose study (Table 1). Seven patients were excluded before receiving the study drug (screening failure), and 2 patients withdrew because of clinical adverse events (see below). An additional two patients were excluded because intravenous access for drawing blood could not be obtained.

The minimum iothalamate clearance values on day −1 and day 6 are shown in Table 4. Peak reductions in iothalamate clearance with rofecoxib, 12.5 mg or 25 mg, compared with placebo were significant (0.14 and 0.13 mL/s, respectively; $P = 0.019$ and 0.029), whereas the reduction in iothalamate clearance with indomethacin compared with placebo (0.10 mL/s) approached significance ($P = 0.086$). Differences between indomethacin and rofecoxib, 12.5 mg or 25 mg, were not significant ($P > 0.2$ in both cases).

Creatinine clearance was also used to determine the effects of rofecoxib, indomethacin, and placebo on peak reduction in glomerular filtration rate (data not shown). No significant differences were observed between any of the treatments or between treatment and placebo when creatinine clearance was used to measure glomerular filtration rate.

Compared with placebo, neither rofecoxib nor indomethacin caused consistent changes in peak reduction in urinary sodium excretion (Table 3). Although rofecoxib, 12.5 mg, caused a significant 34.61% reduction in peak urinary sodium excretion ($P = 0.011$), the effects of rofecoxib, 25 mg, and indomethacin were not significant ($P = 0.119$ and 0.077, respectively). Compared with placebo, treatment with rofecoxib or indomethacin did not significantly change peak reductions in urinary potassium excretion from day -1 to day 6.

Only treatment with indomethacin significantly reduced the minimum serum sodium concentration (3.75% compared with placebo; $P = 0.003$) after drug administration. The effect of indomethacin was significantly greater than that of rofecoxib, 12.5 mg or 25 mg ($P = 0.019$ and 0.007, respectively). In addition, only treatment with indomethacin significantly increased serum potassium concentration (6.16% compared with placebo; $P = 0.045$) after drug administration.

Safety

Glomerular filtration rate was assessed during the 6 hours after the last dose of drug. In many patients, the glomerular filtration rate approached or exceeded baseline values at the end of the 6 hours (data not shown). No substantial statistical adjustment was necessary for baseline glomerular filtration rate before patients entered each crossover period. Therefore, values had returned to baseline before the next treatment was administered. At the 2-week post-study visit, blood urea nitrogen and creatinine levels were measured to assess renal function; these values were at the baseline level in all patients.

Single-Dose Study

One patient in the single-dose study developed hypotension (not requiring treatment) associated with indomethacin administration.

Multiple-Dose Study

In the multiple-dose study, one patient who received indomethacin had a serious adverse event. The patient developed acute severe abdominal pain and was found on surgical exploration to have a perforated viscous. Two patients (both of whom received rofecoxib, 12.5 mg) discontinued treatment because of adverse events that subsequently resolved. One of these patients experienced abdominal pain, constipation, and urinary retention and discontinued therapy on day 6 before drug administration. The second patient had constipation and headache before receiving the first dose; these conditions continued after the drug was administered and resulted in withdrawal from the study.

Body weight did not change significantly during the 6 days of drug administration; the maximum differences between any of the intervention groups and placebo did not exceed 0.5 kg. In addition, no statistically significant changes in blood pressure were observed in the rofecoxib and indomethacin groups.

Table 2. Short-Term Effects of Single Doses of Rofecoxib, Indomethacin, and Placebo on Glomerular Filtration Rate*

Treatment	Patients	Predose Inulin Clearance†	Postdose Minimum Inulin Clearance†	Peak Reduction in Glomerular Filtration Rate†	Difference in Peak Reduction (95% CI)	P Value
	n			mL/s		
Rofecoxib, 250 mg	15	1.59 ± 0.05	0.90 ± 0.04	0.61 ± 0.04‡		
Indomethacin, 75 mg	15	1.46 ± 0.05	0.96 ± 0.04	0.56 ± 0.04‡		
Placebo	15	1.49 ± 0.05	1.14 ± 0.04	0.38 ± 0.04‡		
Rofecoxib vs. indomethacin					0.05 (−0.04 to 0.15)	>0.2
Rofecoxib vs. placebo					0.23 (0.14 to 0.33)	<0.001
Indomethacin vs. placebo					0.18 (0.09 to 0.28)	0.003

* Values expressed with the plus/minus sign are the mean ± SE.
† Least-squares mean calculated by using analysis of variance.
‡ Within-treatment comparison, $P \leq 0.05$.

Table 3. Changes in Urinary and Serum Electrolyte Values after Administration of Rofecoxib, Indomethacin, or Placebo*

Variable	Single-Dose Study			Multiple-Dose Study			
	Rofecoxib, 250 mg	Indomethacin, 75 mg	Placebo	Rofecoxib, 12.5 mg/d	Rofecoxib, 25 mg/d	Indomethacin, 50 mg Three Times Daily	Placebo, Three Times Daily
Urinary sodium excretion							
Absolute change, 100 × mmol Na/s	4.6→0.8	3.9→1.5	4.5→3.5	5.6→3.7	6.6→5.1	6.6→4.9	5.1→5.3
Difference in mean peak percentage reduction compared with placebo, %†	68.35 (41.38 to 95.32)‡	48.95 (21.98 to 75.92)‡		34.61 (14.39 to 49.72)‡	22.82 (−1.37 to 40.91)	25.54 (2.27 to 42.95)	
Urinary potassium excretion							
Absolute change, 100 × mmol K/s	6.1→1.9	5.2→2.2	5.7→2.4	2.1→1.8	1.9→1.7	1.8→1.8	2.0→1.8
Difference in mean peak percentage reduction compared with placebo, %†	11.28 (4.27 to 18.30)‡	6.33 (−0.68 to 13.35)		6.23 (−14.81 to 27.28)	5.45 (−15.60 to 26.50)	−0.79 (−21.84 to 20.26)	
Serum sodium concentration							
Absolute change, mmol/L	134→131	134→130	133→132	131.2→130.8	130.8→131.1	130.4→126.4	130.5→131.3
Difference in mean peak percentage reduction compared with placebo, %†	0.75 (0.08 to 1.41)	1.17 (0.50 to 1.83)‡		0.78 (−1.27 to 2.83)	0.32 (−1.72 to 2.37)	3.75 (1.70 to 5.79)‡	
Serum potassium concentration							
Absolute change, mmol/L	3.7→3.5	3.8→3.5	3.7→3.4	3.3→3.3	3.2→3.3	3.2→3.4	3.3→3.2
Difference in mean peak percentage reduction compared with placebo, %†	−2.30 (−4.24 to −0.37)‡	−4.19 (−6.13 to −2.26)‡		−1.65 (−6.65 to 3.35)	−3.37 (−18.37 to 1.63)	−6.16 (−11.16 to 1.16)‡	

* Values in parentheses are 90% CIs.
† A positive value indicates a reduction.
‡ Value differs significantly from that seen with placebo ($P < 0.05$).

Discussion

We performed two studies of the effects of single or multiple doses of rofecoxib, indomethacin, or placebo on renal function in generally healthy elderly adults. In the single-dose study, the principal finding was that rofecoxib, 250 mg (a dose 5-fold to 20-fold greater than the recommended clinical dose), and indomethacin, 75 mg, produced similar decreases in the inulin-determined glomerular filtration rate (0.23 and 0.18 mL/s, respectively) compared with placebo. In the multiple-dose study, 6 days of therapy with rofecoxib, 12.5 mg/d or 25 mg/d, and indomethacin, 50 mg three times daily, produced similar but more modest decreases in the iothalamate-determined glomerular filtration rate (0.14, 0.13, and 0.10 mL/s, respectively) compared with placebo. In both cases, the effects of rofecoxib and those of indomethacin on glomerular filtration rate did not significantly differ. Similar trends were observed when creatinine clearance was used to measure glomerular filtration rate, although creatinine clearance was less sensitive than inulin or iothalamate as a measure of glomerular filtration rate.

The single-dose study was designed to maximize the opportunity to observe deleterious effects on the kidney as mediated by COX inhibition. Single doses of NSAIDs tend to have larger effects on renal function than long-term administration does (16–19); population-based studies have shown that the prevalence of NSAID-mediated renal impairment is lower than that which would be expected on the basis of short-term single-dose studies (20). In contrast, the multiple-dose study more closely mimicked the doses and regimens that would be used in typical clinical situations. The modes of administration rather than the larger doses probably account for the greater effects of both rofecoxib and indomethacin in the single-dose study. The inverse trend in dose response seen in the multiple-dose study (12.5 mg of rofecoxib reduced glomerular filtration rate more than did 25 mg of rofecoxib) suggests that the differences between the studies were more likely due to the regimens than the doses.

Placement of patients on a low-sodium diet increased the dependence of renal function on prostaglandins (11, 12), thus augmenting the effects of COX inhibitors (which

decrease the availability of these eicosanoids). Although a sodium-replete diet more closely mimics the likely clinical pattern of rofecoxib use, a prescribed diet was used in our studies because the ability to document significant effects on renal function under at-will intake conditions may be diminished (21–23). Indeed, a recent study reported that glomerular filtration rate was not affected when patients received a sodium-replete diet (24). Nonetheless, sodium restriction is more likely to create a situation that more closely approximates the expected findings in patients who have more severely contracted effective intravascular fluid volume (as a result of congestive heart failure, diuretic use, poor oral intake, or cirrhosis, for example), in which similar or more marked reductions in glomerular filtration rate after multiple dosing may become evident.

Because the pharmacokinetics of rofecoxib and indomethacin differ, it was important to ensure that comparisons would not be made at the nadir of effect of one drug and the peak effect of the other drug. Previous studies showed that the decrement in glomerular filtration rate after NSAID use generally tends to occur simultaneously with or before the time to maximum plasma drug concentration (T_{max}) (about 2 to 3 hours for rofecoxib and 1.5 to 2.0 hours for indomethacin) (17). The extended observation period allowed us to capture the T_{max} (and, consequently, the maximal decrease in glomerular filtration rate) of both rofecoxib and indomethacin so that comparisons would be made at the maximal effect of both drugs.

Treatment with rofecoxib and indomethacin tended to

reduce urinary sodium and potassium excretion, but not all changes differed significantly. Although salt and water retention may be observed clinically with long-term administration of NSAIDs, these effects usually predominate in patients who are more prone to sodium retention (such as those with moderate to severe renal insufficiency, cirrhosis with ascites, or congestive heart failure). The absence of consistent effects on urinary electrolyte excretion in studies that documented effects on glomerular filtration rate should not be surprising in light of the observation that the effects of NSAIDs on urinary sodium and potassium excretion are often independent of their effects on glomerular filtration rate (25).

Changes in serum electrolyte levels were usually small and not clinically important. The small decrease in serum sodium concentration probably reflects in part the water loading required by the protocol and the known influence of COX inhibition on increasing the sensitivity of the distal nephron to the free water–retaining effects of antidiuretic hormone. The increase in potassium concentration was probably due to inhibition of renin secretion by NSAIDs, creating a hyporeninemic, hypoaldosteronemic state. No patient developed clinical hyperkalemia. Of greatest importance in our study is that all of these effects were similar when rofecoxib was compared with a traditional NSAID.

A recent study found similar renal effects of celecoxib (10). Our results, the finding that COX-2 is constitutively expressed in the kidney (8), and the accumulated scientific

Table 4. **Effect of Rofecoxib or Indomethacin Therapy on Glomerular Filtration Rate, as Determined by Iothalamate Clearance***

Treatment	Patients	Minimum Iothalamate Clearance on Day −1†	Minimum Iothalamate Clearance on Day 6†	Reduction in Iothalamate Clearance‡	Difference in Reduction (90% CI)	P Value
	n	←——————————————mL/s—————————————→				
Placebo	15	1.28 ± 0.07	1.29 ± 0.07	0.03 ± 0.04		
Rofecoxib, 12.5 mg	15	1.37 ± 0.07	1.20 ± 0.07	0.17 ± 0.04		
Rofecoxib, 25 mg	15	1.24 ± 0.06	1.12 ± 0.06	0.16 ± 0.04		
Indomethacin, 50 mg three times daily	15	1.23 ± 0.06	1.14 ± 0.06	0.13 ± 0.04		
Rofecoxib, 12.5 mg, vs. placebo					0.14 (0.05 to 0.25)	0.019
Rofecoxib, 25 mg, vs. placebo					0.13 (0.03 to 0.23)	0.029
Indomethacin vs. placebo					0.10 (0.00 to 0.21)	0.086
Rofecoxib, 12.5 mg, vs. indomethacin					0.04 (−0.06 to 0.14)	>0.2
Rofecoxib, 25 mg, vs. indomethacin					0.03 (−0.07 to 0.13)	>0.2
Rofecoxib, 25 mg, vs. rofecoxib, 12.5 mg					−0.01 (−0.11 to 0.09)	>0.2

* Values expressed with the plus/minus sign are the mean ± SE.
† Observed values.
‡ Values (least-squares means) calculated by using an analysis of covariance model that adjusted for treatment, site, and baseline glomerular filtration rate. Because values are adjusted, they differ slightly from the differences between the unadjusted observed values.

data imply that COX-2 may serve an essential function in the maintenance of renal hemodynamics and electrolyte homeostasis and that the renal effects observed with celecoxib or rofecoxib are likely to be reproduced throughout this class of medications.

On the basis of our results, predisposed persons (such as those with congestive heart failure, diuretic use, or cirrhosis) may experience decreases in glomerular filtration rate similar to those that we observed, regardless of whether a COX-1/COX-2–nonspecific or COX-2–specific inhibitor is used. In such patients, who have low effective circulating fluid volume, NSAID-induced alterations can result in clinically significant renal insufficiency, which usually reverses upon discontinuation of NSAID therapy. Our results suggest that there are few qualitative differences in renal effects achieved with COX-2 inhibition and the effects observed with inhibition of both COX-1 and COX-2. As a consequence, renal precautions observed with administration of traditional COX-1/COX-2 inhibitors should be also observed for the newer COX-2 inhibitors.

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